REMARKS

In the Office Action dated March 5, 2004, Claims 1-73 are pending. The Examiner has made the Restriction Requirement final. Consequently, claims 1-64 are withdrawn from further consideration as drawn to non-elected subject matter. Claims 65-73 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Martinez-Serrano et al (*J. Neurosci.* 15, 5668-5680, 1995), in view of Svendsen et al (*Exper. Brain Res.* 102, 407-414, 1995) and Fricker et al (*J. Neurosci.* 19, 5990-5005, 1999), and further in view of Li et al (*Current Biol.* 8, 971-974, 1995). The Examiner also states that certified copies of the priority documents could not be found in the parent application, Serial No. 08/808,382.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

With respect to the priority documents, Applicants respectfully submit that certified copies of the priority documents were filed in the parent case, Serial No. 08/808,382, on June 29, 2001. In the Office Action dated January 16, 2003, issued in the parent case, Examiner Ton acknowledged receipt of the certified copies of the priority documents (see page 6 of the Office Action).

In response to the Restriction Requirement, Applicants have canceled claims 1-64 without prejudice. Applicants reserve the right to pursue the subject matter of the canceled claims in a divisional application.

Claim 65 previously depended on claim 40. Applicants have amended claim 65 to incorporate the delineation of claim 40 and to further delineate the undifferentiated ES cells as "undifferentiated or pluripotent human ES cells", as clearly supported by, e.g., original claim 60. Applicants have also added claims 74-77 to depend from claim 65 and to incorporate delineations of claims 41-42, 29 and 60, respectively. No new matter is introduced.

Claims 65-73 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Martinez-Serrano et al. (*J. Neurosci.* 15, 5668-5680, 1995), in view of Svendsen et al. (*Exper. Brain Res.* 102, 407-414, 1995) and Fricker et al. (*J. Neurosci.* 19, 5990-5005, 1999), and further in view of Li et al. (*Current Biol.* 8, 971-974, 1995).

It is observed that the claims are drawn to methods of transplanting ES derived neural progenitor cells in a host, methods of producing a stable graft, and methods of modifying a nervous system of a host. The Examiner contends that at the time the present application was filed, it would have been obvious to one skilled in the art to treat a neurodegenerative disorder, such as a complete fimbria-fornix lesion as shown in Martinez-Serrano, by transplanting into the brain, neural progenitor cells transfected with a DNA sequence encoding NGF, as taught by Martinez-Serrano, thereby modifying the nervous system and producing a stable graft. The Examiner is of the opinion that the neural progenitor cells can be derived by culturing ES cells *in vitro* with a differentiation inducing signal under conditions that are not permissive for stem cell renewal, and do not kill and/or induce unidirectional differentiation, as taught by Li et al. The Examiner also contends that the neural progenitor cells can be further proliferated by culturing in the presence of serum free media containing B27, EGF and bFGF, as taught by Svendsen and Fricker.

Further, the Examiner is of the opinion that these references provide motivation for those skilled in the art to combine the respective teachings. In particular, the Examiner points out that Martinez-Serrano et al. state that their methods provide a means to treat brain lesions requiring the generation of neurons or glial cells. According to the Examiner, Svendsen et al. state that B27 enables a dramatic increase in the number of dividing neural precursor cells; and Fricker et al. teach that EFG and bFGF act cooperatively to promote the proliferation of neural precursor cells. Li et al. allegedly offer a motivation by stating that the development of techniques for producing neural progenitor cells from ES cells would provide a source of cells for transplantation.

It is observed that Martinez-Serrano et al. teach the implantation of CNS-derived neural progenitor cells into a rat having a complete fimbria-fornix lesion. The cells, which had been transfected with a retrovirus comprising a DNA sequence encoding NGF, prevented loss of cholenergic neurons. Applicants respectfully submit that the neural progenitor cells employed by Martinez-Serrano et al. are immortalized cells derived from CNS, in contrast to the neural progenitor cells differentiated from undifferentiated or pluripotent embryonic stem cells, as recited in the present claims. Further, the claims, as presently amended, recite neural progenitor cells derived from "undifferentiated or pluripotent human ES cells", in contrast to rat CNS-derived neural progenitor cells. Applicants respectfully submit that nothing in Martinez-Serrano et al. would have suggested or motivated those skilled in the art to try to obtain neural progenitor cells from undifferentiated or pluripotent human ES cells. Moreover, the teaching of Martinez-Serrano et al., which are directed to rat CNS-derived neural progenitor cells, would not have given one skilled in the art any reasonable expectation that undifferentiated or pluripotent human ES cell-derived neural progenitor cells would survive and function after implantation.

Regarding the Examiner's contention that neural progenitor cells can be derived by culturing ES cells *in vitro*, as taught by Li et al., Applicants respectfully submit that Li et al. merely teach inducing the differentiation of mouse embryonic stem (ES) cells into neural progenitor cells by dissociating embryoid bodies (EB's) formed from aggregating ES cells, and culturing the dissociated EB's in media containing retinoic acid and N2 supplement on a substrate which supports neural cells. Applicants respectfully submit that this reference would not have provided any motivation to those skilled in the art to prepare neuroprogenitor cells from differentiating undifferentiated or pluripotent human embryonic stem cells, as presently claimed. Further, those skilled in the art would not have reasonably expected that the teaching of Li et al., solely directed to mouse ES cells, would successfully apply to human ES cells. It is well known in the art that the handling of human and mouse ES cells can be quite different. For example, the mouse ES cells require leukemia inhibitory factor (LIF) for growth, whereas human ES cells do not.

The Examiner also contends that the neural progenitor cells, derived by using the method of Li et al., can be further proliferated by culturing in the presence of serum free media containing B27, EGF and bFGF, as taught by Svendsen and Fricker.

It is observed that Svendsen et al. teach culturing neural precursor cells extracted from E17 rat embryo mesencephalon and striatum (i.e., partially differentiated embryonic tissue). Applicants respectfully submit that nothing in Svendsen et al. would have suggested to those skilled in the art to apply the culture conditions disclosed herein to neuroprogenitor cells from undifferentiated or pluripotent human embryonic stem cells. Further, those skilled in the art would not have reasonably expected that the conditions disclosed by Svendsen et al. for proliferating neural precursor cells extracted from rat embryo mesencephalon and striatum, would successfully apply to neuroprogenitor cells prepared from undifferentiated or pluripotent human embryonic stem cells.

With respect to Fricker et al., it is observed that this reference teaches the use of bFGF to support continuous cell proliferation of neural progenitor cells. The reference also teaches that EGF and bFGF act cooperatively in promoting the proliferation of neural progenitor cells. Fricker et al. further teach that neural progenitor cells that are injected into the ventricular zone develop into neuronal cells.

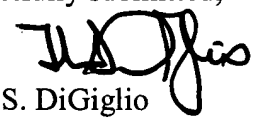
Applicants respectfully submit that the neural progenitor cells referenced in this publication are prepared from human embryonic brain tissue. Applicants respectfully submit that, similar to Svendsen et al., those skilled in the art would not have been motivated to apply the culture conditions disclosed by Fricker et al., directed to differentiated human neural cells, to neuroprogenitor cells prepared from undifferentiated or pluripotent human embryonic stem cells. Further, those skilled in the art would not have reasonably expected that the conditions disclosed by Fricker et al. would successfully apply to neuroprogenitor cells prepared from undifferentiated or pluripotent human embryonic stem cells, as presently recited.

In view of the foregoing amendment and remarks, Applicants respectfully submit that the cited references, taken alone or in combination, do not teach or suggest the claimed methods,

as presently recited. As such, the rejection under 35 U.S.C. §103(a) based on Martinez-Serrano et al., in view of Svendsen et al. and Fricker et al., and further in view of Li et al., is overcome. Withdrawal of the rejection is therefore respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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